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Original Research

Factors predicting hyperimmune response in COVID-19 patients presenting to the emergency department

Prediction of COVID-19 related hyperimmune response

Seref Emre Atıs[1], Mustafa Uguz[2]
[1] Department of Emergency Medicine, Faculty of Medicine, Karabuk University, Karabuk
[2] Department of Infectious Disease, Mersin City Hospital, Mersin, Turkey

Abstract
Aim: The aim of this study is to determine the predictive parameters that can be used in the early determination of hyperimmune response syndrome in the Emergency Department.
Material and Methods: This is a cross-sectional, retrospective study. Patients over the age of 18 who were admitted to the emergency department with a pre-diagnosis of COVID-19, and who were admitted to the intensive care unit were included in the study. Demographic data and laboratory findings were obtained from the hospital information system and patient files. Patients' thoracic computerized tomography images were classified into two groups. The classic involvement includes bilateral basal ground-glass opacities, crazy paving, reverse halo, per lobular pattern, and peripheral consolidation. All other images were included as non-classic COVID-19 involvement.
Results: A total of 202 patients were included. Hyperimmune response development was detected in 74 (36.6%) patients. When laboratory values were examined, ferritin and ALT values were found to be higher, WBC and lymphocyte values were found to be lower in patients who developed a hyperimmune response ($p<0.01$, $p<0.01$, $p=0.038$ and $p=0.004$, respectively). In the logistic regression analysis of the values that can be effective in the development of the hyperimmune response, classic imaging had a statistically significant effect (Odds ratio 0.449 [95% confidence interval, CI = 0.244-0.827], non-classic vs classic[reference]). No statistically significant effect was found in the analysis of other values.
Discussion: Classical chest tomography findings can be useful as a preliminary parameter in the development of hyperimmune response.

Keywords
COVID-19, Emergency, Cytokine, Ferritin, Lymphocyte

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Corresponding Author: Seref Emre Atıs, Sirinevler, Alparslan Cd., No:1, 78200, Karabuk Merkez, Karabuk, Turkey.
E-mail: dremreatis@gmail.com P: +90 506 928 81 86
Corresponding Author ORCID ID: https://orcid.org/0000-0002-5094-6000

Introduction

The SARS-CoV-2 virus emerged as atypical pneumonia cases clustered in China at the end of 2019. The virus spread rapidly between countries and continents in the following months, and the World Health Organization (WHO) declared it as a pandemic. The Coronavirus infectious disease (COVID-19) continues to affect the whole world after two years [1].

Around 6 million cases have been reported worldwide, and the number of cases still increase. Unfortunately, clinical treatment modalities for COVID-19 do not currently exist and clinical studies to identify the treatment are ongoing [2,3].

Currently, the generally accepted view is that hyperimmune response syndrome triggered by SARS-CoV-2 leads to a severe disease course, and treatment efforts are coordinated accordingly [4]. This syndrome caused by COVID-19 has not yet been defined clearly, despite its association with mortality and morbidity [5]. Considering that routine measurement of elevated cytokine levels during a hyperimmune response syndrome at the time of admission is impractical and cost-ineffective, identification of early predictive biomarkers is needed. Unfortunately, parameters such as age, radiological imaging, and comorbidities used to predict disease severity cannot be used with the same efficiency in determining the presence of a hyperimmune response syndrome [6]. Anti-inflammatory treatment approaches to be used in the early stages of a cytokine storm may reduce lung damage and respiratory failure developing throughout the disease course of COVID-19 [7]. Interleukin inhibitors have been used in the early stages of the disease for this purpose [8].

In the present study, we aimed to investigate certain parameters at the time of admission in Emergency Service patients hospitalized in the intensive care unit (ICU) and to examine the relationship between the parameters in the early identification of hyperimmune response syndrome and the need for treatment.

Material and Methods

Study Design:

This research was designed as a cross-sectional, retrospective study. Patients presenting to the Emergency Department of a tertiary hospital between October 31, 2020, and January 01, 2021, were included in the study. Ethics committee approval was obtained for the study (Approval no:2021/740).

Patient Selection:

We included patients aged >18 years who tested positive for COVID-19 via the real-time polymerase chain reaction (rt-PCR) after presenting to the emergency department with a preliminary diagnosis of COVID-19 and were admitted to the intensive care unit (ICU). Patients aged <18 years, those with a negative rt-PCR test result for COVID-19, and patients initially admitted to other units or were discharged were excluded from the study. ICU hospitalization criteria were considered as respiratory rate ≥30/min, severe respiratory distress [dyspnea, use of extra respiratory muscles], oxygen saturation in room air ≤ 90% [PaO2/FiO2 <300 in a patient receiving oxygen]).

Data Collection:

Demographic data (age and sex) and laboratory findings (creatinine, ferritin, fibrinogen, D-dimer, ALT, CRP, procalcitonin, albumin, leukocyte, lymphocyte, neutrophil, and platelet count) were obtained from the hospital information system and patient files. Based on these values, the systemic immune-inflammatory index value (neutrophil value × platelet value/ lymphocyte value) and neutrophil/albumin ratio were calculated for each patient.

Thoracic computed tomography (CT) findings were classified in accordance with the British Society of Thoracic Imaging (BSTI) classification system (available at: http://www.bsti.org.uk/media/resources/files/BSTI_COVID_CT_Proforma_v2_13.04.2020.docx). This system includes four different groups. These are categorized as normal, indeterminate, possible/classic, and non-COVID. The possible/classic involvement classification includes bilateral basal ground-glass opacities, crazy paving, reverse halo, per lobular pattern, and peripheral consolidation. In the present research, patients who were classified as possible/classic according to BTSI criteria were included in the research as classic COVID-19 involvement, and all other classifications were included as non-classic COVID-19 involvement. Hyperimmune response syndrome was considered as patients with prolonged persistent fever despite treatment, elevated CRP or CRP progression during treatment, ferritin elevation, D-dimer elevation, existing lymphopenia, and thrombocytopenia or occurring under treatment, impaired liver function tests, and patients showing a hyperimmune response. The patients were divided into two groups as patients with and without a hyperimmune response.

Primary Outcome:

The primary outcome of this research was to determine the effectiveness of parameters at admission (to the emergency service) in predicting the development of a hyperimmune response in patients hospitalized in the ICU with the diagnosis of COVID-19. The secondary outcome of the research was to identify the correlation between these parameters and mortality.

Statistical analysis:

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analysis of the data obtained in the research. The Shapiro–Wilk test was used to check whether the parameters were normally distributed. Descriptive statistical methods (mean, standard deviation, median and interquartile range, and frequency) were used to present the data. Quantitative parameters were compared between the groups using the Mann–Whitney U test. The Chi-square test was used to compare qualitative parameters between the groups. Logistic regression analysis was used to determine independent parameters affecting the hyperimmune response. $P < 0.05$ indicated statistical significance in all analyses.

Results

Among the 220 patients considered for the study, 18 were excluded owing to missing or incomplete laboratory data. The study was completed with 202 patients, 128 (63.4%) of whom were men. The mean age of patients was 61 years (±15).

A total of 74 (36.6%) patients received treatment as they presented with a hyperimmune response. The mean age of patients with a hyperimmune response was lower than that of patients without a hyperimmune response ($p = 0.025$).

Table 1. Comparison of demographic data and laboratory parameters of patients with and without hyperimmune response

	Hyperimmune Response	Not Hyperimmune Response	p
	n=74 (36.6%)	n=128 (63.4%)	
Age	59 [49-66]	63 [55-75]	0.025¥
Gender (male, n)	53 (71.6%)	75 (58.6%)	0.064Δ
Creatinine (mg/dl)	0.94 [0.80-1.16]	0.97 [0.79-1.47]	0.359
ALT (U/L)	37 [23-70]	23 [16-37]	<0.001
Fibrinogen (mg/dl)	577.00 [447.75-693.5]	523.50 [387.00-666.50]	0.119
D-dimer (mg/L)	1.25 [0.68-2.48]	1.37 [0.82-3.59]	0.331
Ferritin (ng/ml)	648.5 [324.0-1023.0]	220.5 [96.1-477.0]	<0.001
WBC (/microL)	9285 [6087-14027]	10930 [7360-15802]	0.038
Neutrophil (/microL)	7465 [4435-11630]	8670 [5657-13540]	0.096
Platelet (/microL)	210000 [174000-230000]	244000 [167000-320750]	0.221
Lymphocyte (/microL)	775 [442-1215]	1010 [620-1637]	0.004
CRP (mg/dl)	8.09 [3.43-14.70]	6.48 [2.06-14.00]	0.189
Procalcitonin (ng/ml)	0.20 [0.10-0.22]	0.12 [0.04-0.37]	0.325
Albumin (g/dL)	3.60 [3.29-3.81]	3.52 [3.20-3.79]	0.435
Neutrophil /Albumin	2199.89 [1237.70-3291.77]	2599 [1533.66-3889.26]	0.083
SII	2563 [836-5451]	1929 [817-4195]	0.217

¥ The Mann-Whitney U test was used to compare the data, Δ Chi-square test was used to compare the data

Table 2. Hyperimmune response according to CT imaging at the time of admission

	Developing Hyperimmune Response		p
CT Imaging	Positive n=74	Negative n=128	
Classic	43 (58.1%)	47 (36.7%)	0.003*
Not Classic	31 (41.9%)	81 (63.3%)	

* Chi-square test was used to compare the data

Table 3. Logistic regression analysis of parameters that may play a role in the development of hyperimmune response

	Wald	Odds ratio	95% C.I.	
ALT	1.325	1.005	.998	1.017
Ferritin	2.085	1.000	1.000	1.001
WBC	2.529	1.000	1.000	1.000
Lymphocyte	3.619	1.000	.999	1.000
Classic Imaging	6.603*	.449	.244	0.827

Omnibus x2 (5) = 26.54 p<0.001 R2 = 0.169 (Nagelkerke), *p=0.01

Examining laboratory parameters of the patients revealed that ferritin and ALT values were higher ($p < 0.001$ and $p < 0.001$, respectively), whereas WBC and lymphocyte values were lower ($p = 0.038$ and $p = 0.004$, respectively) in patients who developed a hyperimmune response compared with those who did not. Demographic characteristics and laboratory parameters of the patients are summarized in Table 1.

When the thoracic CT scans of the patients at the time of admission were examined, it was found that classic involvement was found in 58.1% of patients who developed a hyperimmune response, while this rate was 36.7% in patients who did not ($p = 0.003$) (Table 2).

In the logistic regression analysis of the values that can be effective in the development of the hyperimmune response, classic imaging had a statistically significant influence (Odds ratio = 0.449 [95% confidence interval, CI = 0.244-0.827], non-classic vs classic [reference]). No statistically significant effect was found in the analysis of other values (Table 3).

Discussion

In the present study, classical CT involvement was more common in patients with the hyperimmune response at admission compared to patients who did not develop a hyperimmune response. Also, in the logistic regression analysis, the non-classical CT imaging had a negative influence on the development of a hyperimmune response. A significant correlation was found between the severity of CT findings and the course of COVID-19 and inflammatory cytokine levels [9,10]. Jin et al. graded computered tomography imaging from 0 (normal) to 4 (several stages of pneumonia) in COVID-19 patients. They found that clinical outcomes were worse in the high-grade group [11]. In another study, it was determined that high initial lung CT scores of the patients were an independent risk factor for patient discharge (Odds ratio = 0.41 [95% confidence interval, CI = 0.18-0.92]) [12].

In the present study, the WBC and lymphocyte levels at the time of admission to the hospital were lower in patients who developed hyperimmune response syndrome in the ICU compared with those who did not. Consistent with this finding, in a systematic review of 3939 patients in 28 different studies, the change in WBC and lymphocyte levels was examined in patients with mild and severe SARS-COV-2 infection and it was found that lymphocyte levels were significantly lower in severe patients [13]. Caricchio et al. found that ALT values were higher and lymphocyte levels were lower in patients who developed a hyperimmune response compared with those who did not [14]. Zhou et al. investigated the role of biochemical parameters in predicting the severity of COVID-19 and reported that a high ferritin level was useful in predicting severe disease [15]. Similarly, in a meta-analysis conducted by Cheng et al., it was reported that a ferritin level above 397 ng/ml was associated

with severe COVID-19 disease [16]. However, WBC, lymphocyte, and ferritin values were not detected as independent factors according to logistic regression analysis. This discordance can be explained by the fact that the present study was conducted among patients already followed in the ICU, whereas the abovementioned studies compared mild–moderate–severe COVID-19 patients. Considering the severe course of COVID-19 in the patients included in the present research, high WBC, lymphocyte, and ferritin values in both groups are an expected result.

Conclusion:

Classical chest tomography findings can be useful as a preliminary parameter in the development of hyperimmune response. Although WBC and lymphocyte counts are high and ferritin value is low in patients with hyperimmune response, these three parameters are not independent predictors for its the development.

Limitations:

This research was designed as a retrospective study and conducted in a single center. The patients' comorbidities were not included in the study. Patients admitted to the ward were not included in the study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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